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(54) Title: DOPAMINE AGONISTS IN COMBINATION WITH NITRIC OXIDE DONORS, COMPOSITIONS AND METHODS OF USE

(57) Abstract

The present invention is directed to novel compositions comprising at least one dopamine agonist in combination with at least one nitric oxide donor (i.e. compounds that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium–derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase). The novel compositions may optionally comprise at least one therapeutic agent, such as, a vasoactive agent, an antimetic agent, and mixtures thereof. The dopamine agonist is preferably apomorphine. The present invention is also directed to methods for treating and/or preventing sexual dysfunctions and/or enhancing sexual responses in patients. In other embodiments, the present invention is directed to methods treating or preventing neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinaemia or myopia. The compounds and/or compositions of the present invention can also be provided in the form of a pharmaceutical kit.

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DOPAMINE AGONISTS IN COMBINATION WITH NITRIC OXIDE DONORS, COMPOSITIONS AND METHODS OF USE

RELATED APPLICATIONS

This application claims priority to U. S. Provisional Application No. 60/123,920 filed March 12, 1999

FIELD OF THE INVENTION

The present invention describes the combination of dopamine agonists and nitric oxide donors (i.e. compounds that donate, transfer or release nitric oxide, elevate endogenous levels of endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase) and novel compositions comprising at least one dopamine agonist and at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and/or at least one therapeutic agent, such as a vasoactive agent, an antimetic agent, and mixtures thereof. The dopamine agonist is preferably apomorphine. The present invention also provides methods for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females, and for treating or preventing neurodegenerative diseases, mitochondrial diseases, spinal cord injury, central or psychostimulant addiction, senile dementia, circulatory disorders, cardiovascular disorders, hyperprolactinaemia or myopia. The compounds and/or compositions of the present invention can be provided in the form of a pharmaceutical kit.

BACKGROUND OF THE INVENTION

Adequate sexual function is a complex interaction of hormonal events and psychosocial relationships. There are four stages to sexual response as described in the *International Journal of Gynecology & Obstetrics*, 51(3):265-277 (1995). The first stage of sexual response is desire. The second stage of sexual response is arousal. Both physical and emotional stimulation may lead to breast and genital vasodilation and clitoral engorgement (vasocongestion). In the female, dilation and engorgement of the blood vessels in the labia and tissue surrounding the vagina produce the "orgasmic platform," an area at the distal third of the vagina where blood becomes sequestered. Localized perivaginal swelling and vaginal

lubrication make up the changes in this stage of sexual response. Subsequently, ballooning of the proximal portion of the vagina and elevation of the uterus occurs. In the male, vasodilation of the cavernosal arteries and closure of the venous channels that drain the penis produce an erection. The third stage of sexual response is orgasm, while the fourth stage is resolution. Interruption or absence of any of the stages of the sexual response cycle can result in sexual dysfunction. One study found that 35% of males and 42% of females reported some form of sexual dysfunction. Read et al, *J. Public Health Med.*, 19(4):387-391 (1997).

While there are obvious differences in the sexual response between males and females, one common aspect of the sexual response is the erectile response. The erectile response in both males and females is the result of engorgement of the erectile tissues of the genitalia with blood which is caused by the relaxation of smooth muscles in the arteries serving the genitalia.

In both pre-menopausal and menopausal females, sexual dysfunction can include, for example, sexual pain disorders, sexual desire disorders, sexual arousal dysfunction, orgasmic dysfunction, dyspareunia, and vaginismus. Sexual dysfunction can be caused, for example, by pregnancy, menopause, cancer, pelvic surgery, chronic medical illness or medications.

In males, some pharmacological methods of treating sexual dysfunctions are available, however, such methods have not proven to be highly satisfactory or without potentially severe side-effects. Papaverine now widely used to treat impotence, is generally effective in cases where the dysfunction is psychogenic or neurogenic and where severe atherosclerosis is not involved. Injection of papaverine, a smooth muscle relaxant, or phenoxybenzamine, a non-specific antagonist and hypotensive, into corpus cavernosum has been found to cause an erection sufficient for vaginal penetration, however, these treatments are not without the serious and often painful side effect of priapism. Also, in cases where severe atherosclerosis is not a cause of the dysfunction, intracavernosal injection of phentolamine, an α-adrenergic antagonist, is used. As an alternative or, in some cases an adjunct to phosphodiesterase inhibition or α-adrenergic blockade for the treatment of erectile dysfunction, prostaglandin E_1 (PGE_1) has been administered to the penis or by intracavernosal injection. A major side

effect frequently associated with intracorpral or transurethral delivered PGE_1 is penile pain and burning. In addition, priapism, infection, penile corporal fibrosis, fibrotic nodules, hypotension, bruising and hematomas may occur. Swelling and ulceration of the penile skin at the site of injection have also been reported.

There is a need in the art for the treatment of sexual dysfunctions, particularly treatments that do not have the undesirable side effects of those agents currently being used. The present invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

Nitric oxide (NO) has been shown to mediate a number of actions including the bactericidal and tumoricidal actions of macrophages and blood vessel relaxation of endothelial cells. NO and NO donors have also been implicated as mediators of nonvascular smooth muscle relaxation. As described herein, this effect includes the dilation of the corpus cavernosum smooth muscle, an event involved in the sexual response process in both males and females. However, the effects of dopamine agonists in combination with nitric oxide donors have not been previously investigated.

In the process of arriving at the present invention, it was unexpectedly discovered that the adverse effects associated with the use of dopamine agonists, specifically apomorphine, for the treatment of sexual dysfunctions can be avoided by the use of the dopamine agonist in combination with nitric oxide donors. Such adverse effects include nausea, diaphoresis, dizziness, double or blurred vision, facial flushing, decrease in both heart rate and blood pressure, pale or ashen coloring and yawning. The smooth muscle relaxant properties of compounds that donate, release or transfer nitrogen monoxide or elevate levels of endogenous nitric oxide or endothelium-derived relaxing factor (EDRF) or are substrates for nitric oxide synthase work together to permit the same efficacy with lower doses of the dopamine agonist.

One embodiment of the present invention provides compositions comprising at least one dopamine agonist and at least one compound that donates, transfers or releases nitrogen monoxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•),

and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The present invention also provides for such compositions in a pharmaceutically acceptable carrier.

Another embodiment of the present invention provides compositions comprising at least one dopamine agonist, at least one compound that donates, transfers or releases nitrogen monoxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase, and at least one therapeutic agent. The invention also provides for such compositions in a pharmaceutically acceptable carrier.

Yet another embodiment of the present invention provides methods for treating and/or preventing sexual dysfunctions and/or enhancing sexual responses in patients, including males and females, by administering to a patient in need thereof a therapeutically effective amount of at least one dopamine agonist and with at least one compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosonium (NO^+) or nitroxyl (NO-), or as the neutral species, nitric oxide (NO•), and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The methods can further comprise administering a therapeutically effective amount of at least one therapeutic agent. The dopamine agonist, nitric oxide donor and therapeutic agent can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

The present invention also describes methods to treat neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease, mitochondrial diseases, spinal cord injuries with resultant loss of memory and sensory function and concomitant loss of muscular control, central or psychostimulant addictions, senile dementia, circulatory disorders, cardiovascular disoders, hyperprolactinaemia and myopia by administering to a patient in need thereof at least one dopamine agonist and at least one compound that donates, transfers or releases nitric oxide as a charged species or as a neutral species and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase. The methods may further comprise administering at least

one therapeutic agent. The dopamine agonist, nitric oxide donor and therapeutic agent can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

These and other aspects of the present invention are described in detail below.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Patient" refers to animals, preferably mammals, more preferably humans.

"Dopamine agonists" refer to agents which enhance endogenous brain dopamanergic neurotransmission. Such agents include, but are not limited to, inhibitors of metabolic inactivation of dopamine as well as inhibitors of transporters involved in dopamine reuptake into nerve terminals.

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

"Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Transurethral" or "intraurethral" refers to delivery of a drug into the urethra, such that the drug contacts and passes through the wall of the urethra and enters into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

"Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is

expressed at the intended site of action.

"Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo*. "NO donor" also includes compounds that are substrates for nitric oxide synthase.

"Alkyl" refers to a lower alkyl group, a haloalkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Alkynyl" refers to an unsaturated acyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl,

propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl, ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronapthyl, quinuclidyl, 2,6-dioxabicyclo[3.3.0]octane, 7-oxabycyclo[2.2.1]heptyl, 8-azabicyclo[3,2,1]oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 8 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta,1,3-dienyl, and the like.

"Heterocyclic ring or group" refers to a saturated, unsaturated, cyclic or aromatic or polycyclic hydrocarbon group having about 3 to about 12 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary heterocyclic groups include pyrrolyl, 3-pyrrolinyl,4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl,

thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrhydrofuranyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, oxazolindinyl 1,3-dioxolanyl, 2,6-dioxabicyclo[3,3,0]octanyl, 2-imidazonlinyl, imidazolindinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like.

"Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, napthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicylic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkenyl" refers to an unsaturated cyclic hydrocarbon having about 3 to about 10 carbon atoms (preferably about 3 to about 8 carbon atoms, more

preferably about 3 to about 6 carbon atoms) comprising one or more carbon-carbon double bonds.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkoxy" refers to $R_{50}O$-, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, and the like.

"Arylalkoxy or alkoxyaryl" refers to an alkoxy group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4- methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Haloalkoxy" refers to a haloalkyl group, as defined herein, to which is appended an alkoxy group, as defined herein. Exemplary haloalkyl groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

"Oxo " refers to =O.

"Oxy " refers to $-O^- R_{77}^+$ wherein R_{77} is an organic or inorganic cation.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

"Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include metal cations such as for example, sodium, potassium, calcium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to

an alkyl group, as defined herein.

"Amino" refers to $-NH_2$.

"Nitrate" refers to $-O-NO_2$.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to $-S-NO_2$.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

"Nitro" refers to the group $-NO_2$ and "nitrosated" refers to compounds that have been substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

"Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Alkylamino" refers to $R_{50}NH-$, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino, cyclohexylamino, and the like.

"Arylamino" refers to $R_{55}NH-$, wherein R_{55} is an aryl group, as defined herein.

"Dialkylamino" refers to $R_{50}R_{52}N-$, wherein R_{50} and R_{52} are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to $R_{55}R_{60}N-$, wherein R_{55} and R_{60} are each independently an aryl group, as defined herein.

"Alkylarylamino" refers to $R_{50}R_{55}N-$, wherein R_{50} is an alkyl group, as defined herein, and R_{55} is an aryl group, as defined herein.

"Aminoalkyl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein.

"Aminoaryl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is

appended an aryl group, as defined herein.

"Thio" refers to –S-.

"Sulfinyl" refers to -S(O)-.

"Methanthial" refers to -C(S)-.

"Thial" refers to =S.

"Sulfonyl" refers to $-S(O)_2-$.

"Sulfonic acid" refers to $-S(O)_2OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation.

"Alkylsulfonic acid" refers to a sulfonic acid group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonic acid" refers to an sulfonic acid group, as defined herein, appended to an aryl group, as defined herein

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, an alkylaryl group or an aryl heterocyclic ring, as defined herein.

"Sulfonamido" refers to $-S(O)_2-N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein, and R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylthio" refers to $R_{55}S-$, wherein R_{55} is an aryl group, as defined herein.

"Cycloalkylthio" refers to $R_{54}S-$, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkylthio groups include cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

"Alkylsulfinyl" refers to $R_{50}-S(O)-$, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyl" refers to $R_{50}-S(O)_2-$, wherein R_{50} is an alkyl group, as defined herein.

"Arylsulfinyl" refers to R_{55}-S(O)-, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyl" refers to R_{55}-$S(O)_2$-, wherein R_{55} is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})$- wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein.

"Ester" refers to $R_{51}C(O)O$- wherein R_{51} is a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein.

"Carbamoyl" refers to -O-$C(O)N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carbamate" refers to $R_{51}O$-$C(O)N(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carboxyl" refers to $-C(O)OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to –C(O)-.

"Alkylcarbonyl" or "alkanoyl" refers to R_{50}-C(O)-, wherein R_{50} is an alkyl group, as defined herein.

"Arylcarbonyl" or "aroyl" refers to R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein.

"Carboxylic ester" refers to -$C(O)OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, an alkylaryl group or an aryl heterocyclic ring, as defined herein.

"Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended

to a carboxyl group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Carboxamido" refers to -C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group or an arylheterocyclic ring, as defined herein, and R_{51} and R_{57} when taken together with the nitrogen to which they are attached form a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

"Urea" refers to -N(R_{59})-C(O)N(R_{51})(R_{57}) wherein R_{51}, R_{57}, and R_{59} are each independently a hydrogen atom, an alkyl group, an aryl group, an alkylaryl group, or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together with the nitrogen to which they are attached form a heterocyclic ring, as defined herein.

"Phosphoryl" refers to -P(R_{70})(R_{71})(R_{72}), wherein R_{70} is a lone pair of electrons, sulfur or oxygen, and R_{71} and R_{72} are each independently a covalent bond, a hydrogen, a lower alkyl, an alkoxy, an alkylamino, a hydroxy or an aryl, as defined herein.

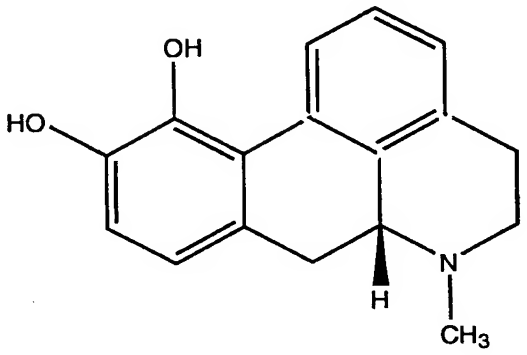
The term "sexual dysfunction" generally includes any sexual dysfunction in a patient, including an animal, preferably a mammal, more preferably a human. The patient can be male or female. Sexual dysfunctions can include, for example, sexual desire disorders, sexual arousal disorders, orgasmic disorders and sexual pain disorders. Female sexual dysfunction refers to any female sexual dysfunction including, for example, sexual desire disorders, sexual arousal dysfunctions, orgasmic dysfunctions, sexual pain disorders, dyspareunia, and vaginismus. The female can be pre-menopausal or menopausal. Male sexual dysfunction refers to any male sexual dysfunctions including, for example, male erectile dysfunction and impotence.

The present invention is directed to the treatment and/or prevention of sexual dysfunctions in patients, including males and females, by administering

the compounds and/or compositions described herein. The present invention is also directed to improving and/or enhancing sexual responses in a patient, including males and females, by administering the compounds and/or compositions described herein. The novel compositions and methods of the present invention are described in more detail herein.

Without intending to be bound by the theory of the invention, the dopamine D2 receptors in the mid-brain region of a patient can be stimulated to a degree sufficient to cause sexual response by the administration of dopamine agonists. Dopamine agonists or agents that enhance brain dopamanergic neurotransmission that can be used in the present invention include, for example, apomorphine, amineptine, N-n-propyl-norapomorphine, bromocriptine, *p*-chlorophenylalanine, *p*-chloromethylamphetamine, D-amphetamine, amatidine, benserazide, botiacrine, bupropion, cabergoline, carmoxirole, clozapine, desocriptine, dihydroergotamine, dihydroergocryptine, dihydroergocristine, α-dihydroergocryptine, dopexamine, dopamine, docarpamine, domperidone, eticlopride, fenfluramine, fenoldopam, haloperidol, ibopamine, L-3,4-dihydroxyphenylalanine (L-DOPA), levodopa, lisuride, lysergin, lergotrile, mazindol, metoclopramide, metergoline, medifoxamine, mesulergine, mosapride, mosapramine, naxagolide, piribedil, pergolide, pramipexole, piroheptine, propylbutyldopamine, quinagolide, quinpirole, riluzole, ropinirole, SKF 38393, SKF 81297, sulpiride, talipexole, trazodone, terguride, tiomergine,and the like. Preferred dopamine agonists for the treatment and/or prevention of sexual dysfunctions are apomorphine, N-n-propyl-norapomorphine, bromocriptine, cabergoline, lisuride, metergoline, naxagolide, pergolide, piribedil, quinagolide, ropinirole, terguride and unergol; more preferably apomorphine, N-n-propyl-norapomorphine, and bromocriptine.

Apomorphine, a short acting dopamine mixed D1/D2 receptor agonist, is the most preferred dopamine agonist. Apomorphine ((R)-5,6,6α,7-tetrahydro-6-methyl-4H-dibenzo-[de,g] quinoline-10,11-diol) is represented by formula (I):



(I)

Apomorphine may exist as a free base or its acid salt. The term "apomorphine" refers to and includes the free base form of apomorphine as well as pharmacologically acceptable acid salts thereof.

In the present invention, the preferred form is apomorphine hydrochloride, however, other pharmacologically acceptable forms can also be utilized. In addition to the hydrochloride salt, other acceptable acid salts include, but are not limited to, hydrobromide, hydroiodide, bisulfate, phosphate, acid phosphate, lactate, citrate, tartarate, salicylate, succinate, maleate, gluconate and the like.

The present invention also encompasses the use of agents that are able to enhance endogenous brain dopamanergic neurotransmission to a degree sufficient to cause a sexual response. Such agents include, but are not limited to, inhibitors of metabolic inactivation of dopamine as well as inhibitors of transporters involved in dopamine reuptake into nerve terminals, serotonin receptor agonists (such as, for example, 1-(2,5-dimethoxy-4-iodophenyl)-1-aminopropane, 5-methoxytryptamine, α-methyl-5-trylptamine, 2-methyl-5-hydroxytryptamine, N-acetyl-5-hydroxytryptamine, buspirone, sumatriptin and the like), oxytocinergic analogues (such as, for example, isotonic, carbetocin, lysine-conoprressin deaminooxytocin, mesotocin, antocin, glumitocin, aspargitocin, valitocin, asvatocin, phasvatocin, seritocin, and the like) and mixtures thereof.

Sources of information for the above compounds include Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Ed.), McGraw-Hill, Inc.

(1996), The Physician's Desk Reference (49th Ed.), Medical Economics (1995), Drug Facts and Comparisons (1993 Ed), Facts and Comparisons (1993), Merck Index on CD-ROM, Twelfth Edition, Version 12:1, (1996), STN Express, file phar and file registry, the disclosures of each of which are incorporated herein by reference in their entirety.

A principal aspect of the present invention relates to novel compositions comprising at least one dopamine agonist, nitric oxide and/or at least one compound that donates, transfers or releases nitric oxide and/or stimulates endogenous production of nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase, and/or otherwise directly or indirectly deliver or transfer nitric oxide to a site of its activity, such as on a cell membrane, *in vivo*.

As used herein, the term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO-). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO•), nitrosonium (NO^+) does not react with O_2 or O_2^- species, and functionalities capable of transferring and/or releasing NO^+ and NO- are also resistant to decomposition in the presence of many redox metals.

Compounds contemplated for use in the present invention (e.g., dopamine agonist) can be used in combination with nitric oxide and compounds that release nitric oxide (i.e., compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer nitric oxide to a site of its activity, such as on a cell membrane, and/or elevate or stimulate production of endogenous nitric oxide or EDRF *in vivo* and/or is a substrate for nitric oxide synthase

The term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds include any and all such compounds which provide nitrogen monoxide to its intended site of action in a form active for its intended purpose. The term "NO adducts" encompasses

any nitrogen monoxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines (NONOates), (E)-alkyl-2-[(E)-hydroxyimino]-5-nitro-3-hexene amines or amides, nitrosoamines, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide. The "NO adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated or a combination thereof at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

One group of NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars; S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, 15(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the present invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine and S-nitroso-glutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and

serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and cytokines. Such nitrosylated proteins are described in WO 93/09806, the disclosure of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; and

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q , or $(C(R_e)(R_f))_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-CH_2\text{-}C(T\text{-}Q)(R_e)(R_f)$, or $-(N_2O_2\text{-})^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2\text{-}C(T\text{-}Q)(R_e)(R_f)$ or $-(N_2O_2\text{-})\bullet M^+$; then

"-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

In cases where R_e and R_f are a heterocyclic ring or R_e and R_f when taken together with the carbon atoms to which they are attached are a heterocyclic ring, then R_i can be a substituent on any disubstituted nitrogen contained within the radical wherein R_i is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetraflurorborate in an inert solvent.

Another group of NO adducts for use in the present invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O-, ON-N- or ON-C- group. The compounds that include at least one ON-O-, ON-N- or ON-C- group are preferably ON-O-, ON-N- or ON-C-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O, ON-N- or ON-C-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O-, ON-N- or ON-C-sugars; ON-O-, ON-N- or ON-C-modified or unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O-, ON-N- or ON-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of NO adducts for use in the present invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group. Preferred among these compounds are O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-,

O_2N-N-, O_2N-S- or O_2N-C- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C-sugars; O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityltetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol and propatylnitrate.

Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: R^1R^2-N(O-M^+)-NO, where R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is as defined herein.

Another group of NO adducts are thionitrates that donate, transfer or release nitric oxide and are represented by the formula: R^1-(S)-NO_2, where R^1 is a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group. Preferred are those compounds where R^1 is a polypeptide or hydrocarbon with a pair or pairs of thiols that are sufficiently structurally proximate, i.e., vicinal, that the pair of thiols will be reduced to a disulfide. Compounds which form disulfide species release nitroxyl ion (NO-) and uncharged nitric oxide (NO•).

The present invention is also directed to compounds that stimulate endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are substrates for the enzyme, nitric oxide synthase. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, including their nitrosated and nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine and nitrosylated

L-homoarginine), precursors of L-arginine and/or physiologically acceptable salts thereof, including, for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid) and the substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

The present invention is also based on the discovery that the administration of at least one dopamine agonist, at least one therapeutic agent and at least one nitric oxide donor described herein, are effective for treating or preventing sexual dysfunctions or enhancing sexual responses in patients, including males and females. The therapeutic agents of the present invention, include, but are not limited to vasoactive agents and antiemetic agents. For example, the patient can be administered a therapeutically effective amount of at least dopamine agonist, and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one dopamine agonist, and at least one therapeutic agent, and, optionally, at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a substrate for nitric oxide synthase. The compounds can be administered separately or as components of the same composition.

A vasoactive agent is any therapeutic agent capable of relaxing vascular smooth muscle. Suitable vasoactive agents include, but are not limited to, potassium channel activators (such as, for example, nicorandil, pinacidil, cromakalim, minoxidil, aprilkalim, loprazolam and the like); calcium channel blockers (such as, for example, nifedipine, veraparmil, diltiazem, gallopamil, niludipine, nimodipins, nicardipine, and the like); ß-blockers (such as, for example, butixamine, dichloroisoproterenol, propanolol, alprenolol, bunolol, nadolol, oxprenolol, perbutolol, pinodolol, sotalol, timolol, metoprolol, atenolol,

acebutolol, bevantolol, pafenolol, tolamodol, and the like); long and short acting α-adrenergic receptor antagonist (such as, for example, phenoxybenzamide, dibenamine, doxazosin, terazosin, phentolamine, tolazoline, prozosin, trimazosin, yohimbine, moxisylyte and the like); phosphodiesterase inhibitors (such as, for example, papaverine, zaprinast, sildenafil, IC 351); adenosine, ergot alkaloids (such as, for example, ergotamine, ergotamine analogs, including, for example, acetergamine, brazergoline, bromerguride, cianergoline, delorgotrile, disulergine, ergonovine maleate, ergotamine tartrate, etisulergine, lergotrile, lysergide, mesulergine, metergoline, metergotamine, nicergoline, pergolide, propisergide, proterguride, terguride and the like); vasoactive intestinal peptides (such as, for example, peptide histidine isoleucine, peptide histidine methionine, substance P, calcitonin gene-related peptide, neurokinin A, bradykinin, neurokinin B, and the like); prostaglandins (such as, for example, PGE_1, PGA_1, PGB_1, PGF_1, PGF_2, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, prostacyclins, thromboxanes, leukotrienes, 6-keto-PGE_1 derivatives and carbacyclin derivatives, and the like); semi-synthetic or synthetic derivatives of natural prostaglandins (such as, for example, carboprost tromethamine, dinoprost tromethamine, dinoprostone, gemeprost, metenoprost, sulprostone, triprost, isoprostanes, and the like); opioid antagonists (such as, for example, naltrexone, naloxone, and the like); endothelin antagonists (such as, for example, bosentan, sulfonamide endothelin antagonists, BQ-123, SQ 28608, and the like) and mixtures thereof.

Preferred are combinations of at least one dopamine agonist (such as, for example, apomorphine, N-n-propyl-norapomorphine or bromocriptine), and at least one nitric oxide donor (such as L-arginine, N-hydroxy-L-arginine or S-nitroso-glutathione) with at least one α-blocker (such as, for example, phentolamine, prazosin, doxazosin, terazosin, yohimbine and/or moxisylyte or a pharmaceutically acceptable salt thereof) and/or at least one phosphodiesterase inhibitors (such as, for example, papaverine, zaprinast, sildenafil and/or IC 351 or a pharmaceutically acceptable salt thereof). Most preferred are combinations of apomorphine and NO donors with the α-blockers, phentolamine or yohimbine. The apomorphine is preferably in the form of apomorphine hydrochloride. The NO donor is preferably L-arginine in the form of L-arginine glutamate or a

combination of L-arginine free base and L-glutamic acid. Phentolamine is preferably in the form of phentolamine hydrochloride or phentolamine mesylate, more preferably phentolamine mesylate. Yohimbine is preferably in the form of yohimbine hydrochloride, yohimbine tartarate, yohimbe bark powder or yohimbe bark extract, more preferably yohimbine hydrochloride or yohimbine tartarate.

An antiemetic agent is any agent capable of controlling and/or preventing nausea and vomiting. Antiemetic agents include, but are not limited to, antidopaminergic agents (such as, for example, metoclopramide, phenothiazines, such as, for example chlorpromazine, prochlorperazine, pipamazine, thiethylperazine, oxypendyl hydrochloride, and the like), serotonin or 5-hydroxytryptamine antagonists (such as, for example, domperidone, odansteron (ZOFRAN®), and the like), histamine antagonists (such as, for example, buclizine hydrochloride, cyclizine hydrochloride, dimenhydrinate, and the like), parasympathetic depressants (such as, for example, scopolamine, and the like), metopimazine, trimethobenzamide, benzquinamine hydrochloride, diphenidol hydrochloride, and mixtures thereof.

The treatment and/or prevention of sexual dysfunctions and/or enhancement of sexual responses in patients using dopamine agonists, specifically apomorphine, has been previously described. For example, U.S. Patent Nos. 5,562,917, 5,624,677, 5,770,606, 5,773,020, 5,888,534, 5,939,094, 5,945,117, 5,994,363, 5,985,889 and WO 98/31368, WO 99/38467 and WO 99/62502 describe the treatment of sexual impotence in humans by administering apomorphine; U. S. Patent Nos. 6,011,043, 6,001,845 and WO 99/65475 describe methods for treating sexual dysfunction using a combination of apomorphine and phentolamine. The disclosure of each of these patents, applications and publications is incorporated by reference herein in their entirety. None of these references, however, disclose, suggest or provide motivation to combine a compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase with apomorphine or apomorphine and phentolamine for treating or preventing sexual dysfunctions, and none of these references disclose or suggest the synergistic or superior effects

that are unexpectedly achieved by combining a compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase with apomorphine or apomorphine and phentolamine for treating or preventing sexual dysfunctions, as claimed herein.

Another embodiment of the present invention provides methods to treat neurodegenerative diseases (such as, for example, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and the like) (U.S. Patent No. 4,970,200; Merello et al, *Mov. Disord.*, 14(1):45-49 (1999)); mitochondrial diseases (such as, for example, Kearns-Sayre Syndrome, Merff Syndrome, Melas Syndrome, Leber's disease, and the like), (WO 95/19170); spinal cord injuries, with resultant loss of memory and sensory function and concomitant loss of muscular control (U.S. Patent No. 4,742,954); central or psychostimulant addictions ((U.S. Patent No. 4,521,421; Halvorsen et al, *Int. J. Addict.*, 13(3):475-484 (1978)); senile dementia ((U.S. Patent No. 5,744,476; Cummings, *Eur. Neurol.*, 28 (suppl, 1):15-23 (1988)); circulatory disorders; cardiovascular disorders (such as, for example, acute and chronic congestive heart failure, chronic cerebrovascular disease, and the like); hyperprolactinaemia (such as, for example, prolactin release inhibitors, lactation suppressant agents, and the like) (Muller et al., *Drugs*, 25(4):399-432 (1983) and myopia (Czepita, *Klin Oczna.*, 101(2):145-147 (1999)) by administering to a patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. The disclosure of each of these patents and publications is incorporated by reference herein in their entirety. These methods may further comprise administering at least one therapeutic agent, preferably a vasoactive agent, such as an ergot alkaloid, as described herein. For example, the patient can be administered a therapeutically effective amount of at least one dopamine agonist and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide or is a substrate for nitric oxide synthase. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one dopamine agonist, at least one therapeutic agent, and at least one compound that donates, transfers or releases nitric oxide, or elevates levels of endogenous EDRF or nitric oxide, or is a

substrate for nitric oxide synthase. The dopamine agonists, nitric oxide donors and/or therapeutic agents can be administered separately or in the form of a composition. The compounds and compositions of the present invention can also be administered in combination with other medications used for the treatment of these disorders.

When administered *in vivo*, the compositions of the present invention may be administered with pharmaceutically acceptable carriers and in dosages described herein. When the compositions of the present invention are administered as a mixture of at least one dopamine agonist and at least one nitric oxide donor, they can also be used in combination with one or more additional compounds (e.g., therapeutic agents). When administered separately, the nitric oxide donor(s) and/or therapeutic agent can be administered simultaneously with, subsequently to, or prior to administration of the dopamine agonist(s) and/or other additional compound(s) to prevent or treat the diseases described herein.

The compounds and compositions of the present invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation spray, by topical application, by injection into the corpus cavernosum tissue, by transurethral drug delivery, transdermally, vaginally, or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Parenteral includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion techniques. Parenteral also includes injection into the corpus cavernosum tissue, which can be conducted using any effective injection system including, but not limited to, conventional syringe-and-needle systems or needleless injection devices.

Transdermal drug administration, which is known to one skilled in the art, involves the delivery of pharmaceutical agents via percutaneous passage of the drug into the systemic circulation of the patient. Topical administration, which is well known to one skilled in the art, involves the delivery of pharmaceutical agents via percutaneous passage of the drug into the systemic circulation of the patient. Topical administration includes vaginal

administration, vulval administration, penile administration and rectal administration. Topical administration can also involve transdermal patches or iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Topical administration also includes administering the compounds and compositions to the eyes, particularly for the treatment of glaucoma.

Dosage forms for topical administration of the compounds and compositions of the present invention preferably include creams, sprays, lotions, gels, ointments, emulsions, coatings for condoms, liposomes, foams, and the like. Administration of the cream, spray, lotion, gel, ointment, emulsion, coating, liposome, or foam can be accompanied by the use of an applicator or by transurethral drug delivery using a syringe with or without a needle or penile insert or device, or by clitoral, vulval or vaginal delivery, and is within the skill of the art. Typically a lubricant and/or a local anesthetic for desensitization can also be included in the formulation or provided for use as needed. Lubricants include, for example, K-Y jelly (available from Johnson & Johnson) or a lidocaine jelly, such as XYLOCAINE® 2% jelly (available from Astra Pharmaceutical Products). Local anesthetics include, for example, novocaine, procaine, tetracaine, benzocaine and the like.

Solid dosage forms for oral administration can include capsules, tablets, effervescent tablets, chewable tablets, pills, powders, effervescent powders, sachets, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the present invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as lactose, saccharose,

sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at body temperature, such that they will melt and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium.

The compounds and compositions of the present invention will typically be administered in a pharmaceutical composition containing one or more carriers or excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Examples of pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, silicone, waxes, petroleum jelly, vegetable oils, polyethylene glycols, propylene glycol, liposomes, sugars, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The compositions can also include one or more permeation enhancers including, for example, dimethylsulfoxide (DMSO), dimethyl formamide (DMF), N,N-dimethylacetamide (DMA), decylmethylsulfoxide (C10MSO), polyethylene

glycol monolaurate (PEGML), glyceral monolaurate, lecithin, 1-substituted azacycloheptan-2-ones, particularly 1-N-dodecylcyclazacylcoheptan-2-ones (available under the trademark Azone™ from Nelson Research & Development Co., Irvine, CA), alcohols and the like.

The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents which do not deleteriously react with the active compounds, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances, and the like. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the present invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailabilty of the compositions can be enhanced by micronization of the formulations using conventional techniques such as grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as phospholipids or surfactants. The bioavailability and absorption of the dopamine agonists can be increased by the addition of tabletting excipients, such as, for example β-cyclodextrin, a β-cyclodextrin derivative, such as for example,

hydroxypropyl-β-cyclodextrin (HPBCD), and the like.

The compounds and compositions of the present invention can be formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitric (nitrate salt), nitrous (nitrite salt), carbonic, sulfuric and phosphoric acid and the like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesuifonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

"Therapeutically effective amount" refers to the amount of the dopamine agonist, nitric oxide donor and/or therapeutic agent which is effective to achieve its intended purpose. While individual patient needs may vary, determination of optimal ranges for effective amounts of each nitric oxide adduct is within the skill of the art. Generally the dosage regimen for treating a condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical

condition of the patient, the severity of the dysfunction, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination and can be adjusted by one skilled in the art. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth herein.

The amount of a given dopamine agonist which will be effective in the treatment of a particular dysfunction or condition will depend on the nature of the dysfunction or condition, and can be determined by standard clinical techniques, including reference to Goodman and Gilman, supra; The Physician's Desk Reference, supra; Medical Economics Company, Inc., Oradell, N.J., 1995; and Drug Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be used in the formulation will also depend on the route of administration, and the seriousness of the dysfunction or disorder, and should be decided by the physician and the patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, supra.

Particularly preferred methods of administration of the dopamine agonist (e.g., apomorphine) are buccal or sublingual prior to sexual activity and in an amount of about 2 mg to about 12 mg to maintain a plasma level of no more than about 5.5 ng/ml. The sublingual administration takes place over a time period in the range of about 2 to about 10 minutes or longer in the range of about 15 to about 20 minutes. These methods of administration are described in further detail in U.S. Patent Nos. 5,770,606, 5,624,677, 5,945,117, and 5,985,889 and in WO 99/38467 and WO 99/62502. The sublingual dose can also be administered in a dose escalation regiment as described in U. S. Patent No. 5,994,363. Alternatively, the dopamine agonist can be administered in a fast-acting form designed to disperse the compound rapidly in the oral cavity. The dopamine agonist may be used in an amount of about 0.05 to about 50 mg. This method of administration is described in detail in WO 98/31368. The dopamine agonist can also be administered transdermally in the form of a water soluble gel or as a

patch as described in U.S. Patent No. 5,562,917 and 5,939,094 respectively. Another mode of administration of the dopamine agonist is via intranasal administration as described in U.S. Patent No. 5,756,483. The disclosure of each of these patents, applications and publications is incorporated by reference herein in their entirety.

The doses of nitric oxide donors in the pharmaceutical composition can be in amounts of about 0.001 mg to about 30 g and the actual amount administered will be dependent on the specific nitric oxide donor compound. For example, when L-arginine is the nitric oxide donor, L-arginine can be administered orally at least one hour prior to sexual activity in an amount of about 0.25 grams to about 10 grams (equivalent to about 0.5 grams to about 20 grams of L-arginine glutamate), preferably about 2 grams to about 4 grams (equivalent to about 4 grams to about 8 grams of L-arginine glutamate); more preferably about 2.5 grams to about 3.5 grams (equivalent to about 5 grams to about 7 grams of L-arginine glutamate); most preferably about 3 grams (equivalent to 6 grams of L-arginine glutamate).

The α-antagonist, such as phentolamine, can be administered in amounts of about 3.7 mg to about 90 mg (equivalent to about 5 mg to about 120 mg phentolamine mesylate), preferably about 22 mg to about 37 mg (equivalent to about 30 mg to about 50 mg phentolamine mesylate), more preferably about 26 mg to about 34 mg (equivalent to about 35 mg to about 45 mg phentolamine mesylate), even more preferably about 28 mg to about 31 mg (equivalent to about 38 mg to about 42 mg phentolamine mesylate), most preferably about 30 mg (equivalent to about 40 mg phentolamine mesylate).

The α-antagonist, such as yohimbine, can be administered in an amount of about 1.0 mg to about 18.0 mg (equivalent to about 1.1 mg to about 19.8 mg yohimbine hydrochloride), preferably about 4.5 mg to about 6.4 mg, (equivalent to about 5.0 mg to about 7.0 mg yohimbine hydrochloride), more preferably about 5.0 mg to about 6.0 mg, (equivalent to about 5.5 mg to about 6.5 mg yohimbine hydrochloride), most preferably about 5.5 mg (equivalent to about 6.0 mg yohimbine hydrochloride). The yohimbine can also be administered in the form of its pharmaceutical salt, yohimbine tartarate, or yohimbe bark powder or extract that has been standardized to deliver up to about 18 mg of yohimbine.

The present invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the present invention, including, at least one dopamine agonist, one or more NO donors, and one or more therapeutic agents described herein. Such kits can also include, for example, other compounds and/or compositions (e.g., permeation enhancers, lubricants, and the like), a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which instructions can also reflects approval by the agency of manufacture, use or sale for human administration.

The disclosure of each patent, patent application and publication cited or described in the specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention without departing from the spirit and scope thereof.

CLAIMS

What is claimed is:

1. A composition comprising at least one dopamine agonist, or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, or a pharmaceutically acceptable salt thereof.

2. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

3. The composition of claim 1, wherein the at least one dopamine agonist is apomorphine, amineptine, N-n-propyl-norapomorphine, bromocriptine, *p*-chlorophenylalanine, *p*-chloromethylamphetamine, D-amphetamine, amatidine, benserazide, botiacrine, bupropion, cabergoline, carmoxirole, clozapine, desocriptine, dihydroergotamine, dihydroergocryptine, dihydroergocristine, α-dihydroergocryptine, dopexamine, dopamine, docarpamine, domperidone, eticlopride, fenfluramine, fenoldopam, haloperidol, ibopamine, L-3,4-dihydroxyphenylalanine, levodopa, lisuride, lysergin, lergotrile, mazindol, metoclopramide, metergoline, medifoxamine, mesulergine, mosapride, mosapramine, naxagolide, piribedil, pergolide, pramipexole, piroheptine, propylbutyldopamine, quinagolide, quinpirole, riluzole, ropinirole, SKF 38393, SKF 81297, sulpiride, talipexole, trazodone, terguride or tiomergine.

4. The composition of claim 3, wherein the at least one dopamine agonist is apomorphine or apomorphine hydrochloride.

5. The composition of claim 1, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

6. The composition of claim 5, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

7. The composition of claim 5, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; and

(iii) H_2N-CH(CO_2H)-(CH_2)$_m$-C(O)NH-CH(CH_2SNO)-C(O)NH-CH_2-CO_2H;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q , or ($C(R_e)(R_f)$)$_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO_2; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)$_o$- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH_2-C(T-Q)(R_e)(R_f), or -(N_2O_2-)$^-$•M^+, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is -CH_2-C(T-Q)(R_e)(R_f) or -(N_2O_2-)•M^+; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

8. The composition of claim 1, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N-, O_2N-S- or -O_2N-C- group;

(iii) a N-oxo-N-nitrosoamine having the formula: R^1R^2-N(O-M^+)-NO, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

9. The composition of claim 8, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypepetide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

10. The composition of claim 8, wherein compound comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-C-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-C-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-C-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, an O_2N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-C-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound, an O_2N-S-heterocyclic compound or an O_2N-C-heterocyclic compound.

11. The composition of claim 1, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

12. The composition of claim 11, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, N-hydroxy-L-arginine, or a pharmaceutically acceptable salt thereof.

13. The composition of claim 12, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine glutamate or a combination of L-arginine and L-glutamic acid.

14. The composition of claim 1, wherein the composition is in a form that can be administered orally, bucally, topically, by injection, by inhalation, by transurethral application or by transdermal application.

15. The composition of claim 14, wherein the composition is administered orally in the form of a solid or liquid dose.

16. The composition of claim 15, wherein the solid dose is a tablet or capsule.

17. The composition of claim 16, wherein the capsule is a sustained release capsule

18. The composition of claim 16, wherein the tablet is a sublingual tablet.

19. The composition of claim 14, wherein the composition is in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition that can be administered topically.

20. The composition of claim 14, wherein the composition is in the form of a sustained-release patch that can be administered by transdermal application.

21. The composition of claim 4 wherein the apomorphine is present in an amount of about 2 mg to about 12 mg.

22. The composition of claim 12, wherein the arginine is present in an amount of about 0.25 g to about 10 g.

23. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 1.

24. The method of claim 23, wherein the patient is female.

25. The method of claim 23, wherein the patient is male.

26. The method of claim 23, wherein the composition is administered orally, bucally, topically, by injection, by inhalation, by transurethral application or by transdermal application.

27. The method of claim 26, wherein the composition is administered orally in the form of a solid or liquid dose.

28. The method of claim 27, wherein the solid dose is a tablet or capsule.

29. The method of claim 28, wherein the capsule is a sustained release capsule

30. The method of claim 28, wherein the tablet is a sublingual tablet.

31. The method of claim 26, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

32. The method of claim 26, wherein the composition is administered by transdermal application in the form of a sustained-release patch.

33. A method for treating or preventing a neurodegenerative disease, a mitochondrial disease, a spinal cord injury, a central or psychostimulant addiction, senile dementia, a circulatory disorder, a cardiovascular disorder, hyperprolactinaemia or myopia in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 1.

34. The composition of claim 1, further comprising at least one therapeutic agent or a pharmaceutically acceptable salt thereof.

35. The compositon of claim 34, wherein the therapeutic agent is a vasoactive agent or an antiemetic agent.

36. The composition of claim 35, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α–blocker, a β–blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, an opioid antagonist, an endothelin antagonist or a mixture thereof.

37. The composition of claim 36, wherein the vasoactive agent is an α-blocker or a phosphodiesterase inhibitor.

38. The composition of claim 37, wherein the α-blocker is phentolamine, prazosin, doxazosin, terazosin, yohimbine or moxisylyte and the phosphodiesterase inhibitor is papaverine, zaprinast, sildenafil or IC 351, or a mixture thereof.

39. The compostion of claim 38, wherein the α-blocker is phentolamine or yohimbine.

40. The composition of claim 39, wherein the phentolamine is phentolamine hydrochloride or phentolamine mesylate.

41. The compositon of claim 40, wherein the phentolamine is present in an amount of about 3.7 milligrams to about 90 milligrams.

42. The composition of claim 39, wherein the yohimbine is yohimbine hydrochloride, yohimbine tartarate or a plant extract containing yohimbine.

43. The composition of claim 42, wherein the plant extract containing yohimbine is a yohimbe bark powder or yohimbe bark extract.

44. The composition of claim 42, wherein the yohimbine is present in an amount of about 1 mg to about 18 mg.

45. The composition of claim 43, wherein the plant extract containing yohimbine is present in an amount of up to 18 mg standardized to yohimbine.

46. The compositon of claim 35, wherein the antiemetic agent is an antidopaminergic agent, a serotonin or 5-hydroxytryptamine antagonist, a histamine antagonist, a parasympathetic depressant, metopimazine,

trimethobenzamide, benzquinamine hydrochloride, diphenidol hydrochloride, or a mixture thereof.

47. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 34.

48. The method of claim 47, wherein the patient is female.

49. The method of claim 47, wherein the patient is male.

50. The method of claim 47, wherein the composition is administered orally, bucally, topically, by injection, by inhalation, by transurethral application or by transdermal application.

51. The method of claim 50, wherein the composition is administered orally in the form of a solid or liquid dose.

52. The method of claim 51, wherein the solid dose is a tablet or capsule.

53. The method of claim 52, wherein the capsule is a sustained release capsule

54. The method of claim 52, wherein the tablet is a sublingual tablet.

55. The method of claim 50, wherein the composition is administered topically in the form of a cream, a spray, a lotion, a gel, an ointment, an emulsion, a foam, a coating for a condom, or a liposome composition.

56. The method of claim 50, wherein the composition is administered by transdermal application in the form of a sustained-release patch.

57. A method for treating or preventing a neurodegenerative disease, a mitochondrial disease, a spinal cord injury, a central or psychostimulant addiction, senile dementia, a circulatory disorder, a cardiovascular disorder, hyperprolactinaemia or myopia in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 34.

58. A kit comprising at least one dopamine agonist and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, or a pharmaceutically acceptable salt thereof.

59. The kit of claim 58, wherein the at least one dopamine agonist is apomorphine, amineptine, N-n-propyl-norapomorphine, bromocriptine, *p*-chlorophenylalanine, *p*-chloromethylamphetamine, D-amphetamine, amatidine, benserazide, botiacrine, bupropion, cabergoline, carmoxirole, clozapine, desocriptine, dihydroergotamine, dihydroergocryptine, dihydroergocristine, α-dihydroergocryptine, dopexamine, dopamine, docarpamine, domperidone, eticlopride, fenfluramine, fenoldopam, haloperidol, ibopamine, L-3,4-dihydroxyphenylalanine, levodopa, lisuride, lysergin, lergotrile, mazindol, metoclopramide, metergoline, medifoxamine, mesulergine, mosapride, mosapramine, naxagolide, piribedil, pergolide, pramipexole, piroheptine, propylbutyldopamine, quinagolide, quinpirole, riluzole, ropinirole, SKF 38393, SKF 81297, sulpiride, talipexole, trazodone, terguride or tiomergine.

60. The kit of claim 59, wherein the at least one dopamine agonist is apomorphine or apomorphine hydrochloride.

61. The kit of claim 58, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

62. The kit of claim 61, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

63. The kit of claim 61, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; and

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an

alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, a carbamate, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q , or $(C(R_e)(R_f))_k$-T-Q, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o$- or $-N(R_a)R_i$-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, $-CH_2-C(T-Q)(R_e)(R_f)$, or $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the proviso that when R_i is $-CH_2-C(T-Q)(R_e)(R_f)$ or $-(N_2O_2-)\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

64. The kit of claim 58, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N-, O_2N-S- or $-O_2N$-C- group;

(iii) a N-oxo-N-nitrosoamine having the formula: R^1R^2-N(O-M^+)-NO, wherein R^1 and R^2 are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

65. The kit of claim 64, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypepetide,

an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

66. The kit of claim 64, wherein compound comprising at least one O_2N-O-, O_2N-N-, O_2N-S- or O_2N-C- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-C-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-C-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-C-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-oligonucleotide, an O_2N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-C-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound, an O_2N-S-heterocyclic compound or an O_2N-C-heterocyclic compound.

67. The kit of claim 58, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

68. The kit of claim 67, wherein the at least one compound that

donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, N-hydroxy-L-arginine, or a pharmaceutically acceptable salt thereof.

69. The kit of claim 68, wherein the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine glutamate or a combination of L-arginine and L-glutamic acid.

70. The kit of claim 58, further comprising at least one therapeutic agent.

71. The kit of claim 70, wherein the therapeutic agent is a vasoactive agent or an antiemetic agent.

72. The kit of claim 71, wherein the vasoactive agent is a potassium channel activator, a calcium channel blocker, an α–blocker, a β–blocker, a phosphodiesterase inhibitor, adenosine, an ergot alkaloid, a vasoactive intestinal peptide, a prostaglandin, an opioid antagonist, an endothelin antagonist or a mixture thereof.

73. The kit of claim 72, wherein the vasoactive agent is an α-blocker or a phosphodiesterase inhibitor.

74. The kit of claim 71, wherein the antiemetic agent is an antidopaminergic agent, a serotonin or 5-hydroxytryptamine antagonist, a histamine antagonist, a parasympathetic depressant, metopimazine, trimethobenzamide, benzquinamine hydrochloride, diphenidol hydrochloride, or a mixture thereof.

75. The kit of claim 58, wherein the dopamine agonist and the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase are separate components in the kit.

76. The kit of claim 58, wherein the dopamine agonist and the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor,

or is a substrate for nitric oxide synthase are in the form of a composition in the kit.

77. A method for treating a sexual dysfunction in a patient in need thereof comprising administering to the patient at least one dopamine agonist and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase.

78. The method of claim 77, further comprising administering to the patient at least one therapeutic agent.

79. A method for treating or preventing a neurodegenerative disease, a mitochondrial disease, a spinal cord injury, a central or psychostimulant addiction, senile dementia, a circulatory disorder, a cardiovascular disorder, hyperprolactinaemia or myopia in a patient in need thereof comprising administering to the patient at least one dopamine agonist and at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase.

80. The method of claim 79, further comprising administering to the patient at least one therapeutic agent.

81. The method of claim 77 or 79, wherein the at least one dopamine agonist and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are administered separately.

82. The method of claim 77 or 79, wherein the at least one dopamine agonist and the at least one compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase are components of the same composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03709

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/44, 31/495, 31/21, 31/195, 31/16, 31/135, 31/04
US CL :514/284, 250, 288, 509, 562, 563, 565, 614, 649, 654, 740, 742
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/284, 250, 288, 509, 562, 563, 565, 614, 649, 654, 740, 742

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,963,568 A (SCHOENLEBER et al) 16 October 1990, claim 7 in particular.	1-22, 33-46, 57-76, 79-82
Y	US 5,770,606 A (EL-RASHIDY et al) 23 June 1998, see particularly the abstract and the claims.	1-32, 34-56, 58-78, 81, 82
Y	US 5,891,459 A (COOKE et al) 06 April 1999, see the claims in particular.	1-22, 33-46, 57-76, 79-82
Y	WO 96/32118 A (THE UNITED STATES OF AMERICA, REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES) 17 October 1996, see the claims in particular.	1-32, 34-56, 58-78, 81, 82

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07 MAY 2000	25 MAY 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer WILLIAM JARVIS Telephone No. (703) 308-1235

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/03709

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

BRS (WEST: USPT, EPAB, JPAB, DWPI)
search terms: dopamine agonist (apomorphine, bromocriptine, etc.), nitric oxide, arginine, impotence, sexual and erectile dysfunction, neurodegeneration, mitochondrial, addiction, dementia, circulatory, cardiovascular, hyperprolactinemia, myopia